REMARKS

I. Preliminary Remarks

Applicants wish to thank the Examiners for the courtesy of the interviews granted on March 29, 2006 and then on March 31, 2006 at which new claim amendments were discussed. It is believed that the following amendments obviate the outstanding rejections and place the claims in order for allowance.

Independent claims 31 and 36 are hereby amended in accordance with the suggestion of Examiner Wang to specify that suitable host cells are transformed with a fusion product comprising an intrabody and a transcriptional activation domain which "transcriptional activation domain is only active as part of a fusion protein comprising an intrabody which is soluble and stable." The claims are further amended to delete the recitation of "irrelevant antigen specificity" but to insert the recitation that "the expression of [a marker protein]is mediated by the interaction of the transcriptional activation domain with a DNA binding domain wherein the interaction of the transcriptional activation domain with the DNA binding domain is not dependent upon the presence of the antigen for which the intrabody is specific." Claim 35 which already recited a fusion protein comprising an intrabody and a DNA binding protein is similarly amended to delete the recitation of "irrelevant antigen specificity" but to insert the recitation that "the activation of transcription is not dependent upon the presence of an antigen for which the intrabody is specific" as suggested by the Examiner.

This language is supported by the specification at page 13, lines 25-30; at page 16, line 24 through page 17, line 5; and Figs. 1a and 1b disclosing the Quality Control System and distinguishes over the prior art methods of record which rely upon binding of the antibody to its corresponding antigen to provide a signal. Rather, such specific binding is irrelevant to practice of the claimed assay as disclosed in the specification.

II. The Subject Matter of the Invention

The present invention is directed to a method of identifying intrabody frameworks and intrabodies which are soluble and stable under selected conditions in the intracellular

environment. The invention is based on the finding that the solubility/stability of a fusion protein comprising a marker protein and an intrabody is dependent on the solubility/stability of the intrabody moiety. Thus, if the intrabody moiety is soluble and stable in the intracellular environment then the marker protein can be detected and cells expressing such a stable fusion protein can be selected. These methods do not involve any interaction between a scFv and its corresponding antigen (an antibody/antigen reaction).

The methods of claims 31, 35 and 36 are therefore based on the finding that the solubility/stability of a fusion protein comprising an intrabody and a signaling system protein is dependent on the solubility/stability of the intrabody moiety. Thus, if the intrabody moiety is soluble and stable in the intracellular environment, then a marker protein can be detected and cells expressing such a stable fusion protein can be selected. These methods do not involve any interaction between a scFv and its corresponding antigen.

Visintin and Hoeffler rely upon the use of the two-hybrid system for the isolation of intrabodies using an antibody/antigen interaction wherein the identification of the intrabodies is based on the interaction between the antibody and its corresponding antigen and does not determine whether an intrabody is soluble and stable in the manner of the invention. While the Visintin and Hoeffler assays will give a positive signal if an intrabody is soluble, stable and specific for the target antigen, they will not give a signal (they report a false negative) when the intrabody is soluble and stable but is not specific for (lacks binding affinity for) the target antigen.

As a means for better understanding the difference between the invention and the prior art, the Examiners' attention is directed to the attached Exhibit A which depicts a comparison between the methods of Visintin and Hoeffler and that of Applicants.

III. The Outstanding Rejections

Claims 31, 33-38 and 42-47 stand rejected under 35 U.S.C. §112 (first paragraph) for failure to comply with the written description requirement and for the introduction of new matter.

Claims 36-38 and 47 stand rejected as being anticipated under 35 U.S.C. §102(e) over Hoeffler et al. US 2003/0017149.

Claims 42 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Visintin in view of Ptashne et al., US 20040014036.

Claims 31, 33, 35-38 and 43-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Visintin.

Claim 34 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Visintin in further view of Martineau, J. Mol. Biol. or Nolan et al. US 6,153,380.

Claims 31, 33-38 and 43-47 are provisionally rejected under the doctrine of obviousness-type double patenting over co-owned, copending application Serial No. 10/169,179.

IV. Patentability Arguments

A. The Rejections Under 35 U.S.C. §112 (First Paragraph) Should Be Withdrawn.

The written description rejections under 35 U.S.C. §112 (first paragraph) should be withdrawn in light of the amendments to independent claims 31, 35 and 36 discussed at the March 31, 2006 Interview and because a review of the specification and figures make clear that the "quality control" assay of the present invention is carried out in a manner in which the detection of the marker protein is not dependent upon the presence of the antigen for which the intrabody is specific. An examination of Paras. 0073-0082 of the specification describes the quality control process depicted in Figs. 1A and 1B and describes practice of the claimed assay in which intrabodies with "essentially identical antigen binding properties" were tested for in vitro solubility and stability. The specification teaches that "[o]nly two out of six tested scFv fragments [having identical antigen binding properties] were soluble and stable enough to activate reporter gene expression in our quality control system." Para 0082. Thus, the skilled reader would appreciate that the currently claimed method is present in the application as originally filed.

The determination of solubility and stability "in selected conditions" is likewise described and enabled. While it may be determined that an intrabody is unstable under a particular set of conditions, such a determination is not a failing of the assay but rather its purpose. Finally, the Action suggests that Applicants have acquiesced in several of the rejections previously made. Such is absolutely not the case. For example, the issue of "soluble and stable in selected conditions" is supported in the specification and was discussed at the Interview conducted August 22, 2005 and was argued at pages 8 and 9 of the previous Response filed August 31, 2005. With respect to the objection to claim 36 discussed at page 3, lines 9-23, clarification is solicited as to what aspect of the claim language is objected to as the Action appears to acknowledge the presence of the objected to language in the disclosure. Clarification is therefore sought in order that the objection might be addressed. Alternatively, it is believed that the claim language suggested by Examiner Wang at the March 31, 2006 Interview and now presented in the amended claims addresses the issues raised in the Action.

B. The Rejections of Claims 31, 33, 35-38 and 43-47 Under 35 U.S.C. §§102 and/or 103 Should Be Withdrawn.

The current Office Action essentially repeats the rejections from the previous Office Action with some elaboration. Reconsideration of the differences between the claimed invention and the prior art and the bases for rejection is solicited because it is believed that the grounds for rejection previously expressed have been rebutted and the new points raised in the most recent Action lack merit.

Of particular importance is that the Action appears to assume that the claimed invention practices the method of Visintin of "screening for intrabodies with CDRS interacting with a specific antigen" (Action page 6, line 22 to page 7, line 3):

> "How else will one determine whether an intrabody is soluble and stable but to react it with an antigen?" (Action page 7, lines 2-3.)

This statement betrays a fundamental misunderstanding of Applicants' invention the very purpose of which is to avoid dependence upon reaction with an antigen and the false negative results that result from such a dependence!

As discussed previously, the prior art rejections over each of Visintin or Hoeffler in light of the secondary references should be withdrawn because both references rely upon the use of the two-hybrid system for the isolation of intrabodies using an antibody/antigen interaction wherein the claimed identification of the intrabodies is based on the interaction between the antibody and its corresponding antigen and does not determine whether an intrabody is soluble and stable as recited by the claims.

While the Visintin and Hoeffler assays will give a positive signal if an intrabody is soluble, stable and specific for the target antigen, they will not give a signal (they will report a false negative) when the intrabody is soluble and stable but is not specific for the target antigen. The Examiners' attention is directed to the attached Exhibit A which depicts a comparison between the methods of Visintin and that of Applicants.

The present Action argues that the claims do not distinguish over the imperfect prior art systems of Visintin and Hoeffler because the claims do not exclude the false negative results produced by the Visintin and Hoeffler systems! The claims need not recite such an exclusion. They need only recite affirmatively. In this regard, the Action states at page 9, lines 4-6:

> "The claims do not recite that a signal is produced when the intrabody does not react with antigen but is stable and soluble."

This is exactly what the claims recite! The claims recite both (1) producing a signal when the intrabody is stable and soluble and does not react with an antigen and (2) producing a signal when the intrabody is stable and soluble and does react with an antigen. (See the claims and see Exhibit A.)

The Action cites the Visintin disclosure at page 1127 and speculates that Visintin "...assayed the solubility and stability (sic) [of the] intrabody prior to antigen reaction." (Action page 9, lines 14-17.) A reading of that portion of Visintin shows that such is not the case. Visintin states:

> We therefore have developed a general antibody-antigen two-hybrid assay system, in which a positive outcome (e.g., activation of His3 or LacZ) depends on the interaction of scFv

> with target antigen under intracellular conditions. (Visintin page 11727, col. 2, lines 31-34, emphasis supplied.)
>
> We therefore have developed an *in vivo* selection scheme for the isolation of intracellular scFv, based on their ability to bind antigen under conditions of intracellular expression. (Visintin, page 11727, col. 2, lines 56-58, emphasis supplied.).

There is no disclosure of methods for testing stability prior to testing for antigen specificity in Visintin and indeed its "Model Selection" system described in the text bridging pages 11726 and 11727 relied upon the use of the AMCVp41/BTN116 bait with the scFvF8-VP16 fusion protein wherein the scFvF8 portion is an anti-AMCV antibody!

Finally, the Action suggests that Applicants have acquiesced in various of the rejections previously made. Such is absolutely not the case. Specifically, Applicants do not acquiesce that somehow the teachings of secondary references (Ptashne, Martineau or Nolan) when combined with either of Visintin or Hoeffler make up for the deficiencies in those primary references and argued this point at page 13 of their previous response. More specifically, Ptashne is directed to use of a two-hybrid system using Gal4 and Gal11p, but does not teach the basic invention of claim 36 from which claim 42 depends. Similarly, Martineau and Nolan are directed to marker proteins but do not teach the invention of claim 31 from which claim 34 depends.

For these reasons, the new points of argument raised in the current Action fail to rehabilitate the rejections previously rebutted.

C. The Provisional Obviousness-type Double Patenting Rejection Should be Deferred.

The provisional obviousness-type double patenting rejection over the related application should be deferred until an indication that the claims in both applications are otherwise allowable. At that time Applicants will consider the allowable claims of each case and will consider either the submission of arguments that the claims are unobvious over each other or the submission of a terminal disclaimer.

CONCLUSION

For the foregoing reasons it is submitted that each of claims 31, 33-38 and 42-47 should now be allowed. Should the Examiners wish to discuss any issues of form or substance in order to expedite allowance of the pending application, they are invited to contact the undersigned attorney of record, Jeffrey S. Sharp, at the number indicated below.

The Commissioner is authorized to charge any fee deficiency required by the paper to Deposit Account No. 13-2855.

Respectfully submitted,

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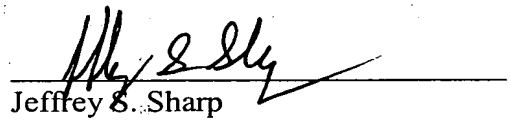
By: 

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EXHIBIT A

Comparison of Visintin et al. and applicant

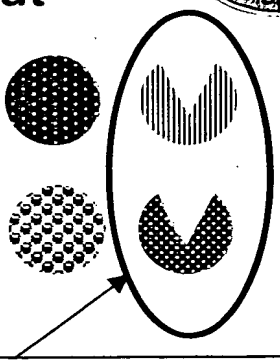
Visintin et al.

Aim: Identification of binders against target

1) Library input

Stable frameworks

Unstable frameworks



Clones in the library with desired specificity against target

2) Screening in yeast

Screening against target:

3) Selection

3.1. Selected with specificity against target:

3.2. Not selected, although specificity against target:

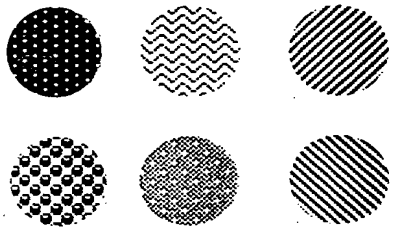
Applicant

Aim: Identification of stable and soluble frameworks

1) Library input

Stable frameworks

Unstable frameworks



2) Screening in yeast

Screening is performed without target to identify stable and soluble frameworks

3) Selection

3.1. Selected due to stability and solubility